



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

November 29, 2001

MEMORANDUM

Subject: Acute Toxicity Review for EPA Reg. No.: 72674-EA
Densil DG45 Fungicide
DP Barcode: D277594
Case No: 070296

To: Marshall Swindell PM 33
Martha Terry, Team Reviewer
Regulatory Management Branch I
Antimicrobials Division (7510C)

From: Robert A. Turpin, Scientist *R.T.*
Chemistry/Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

Through: Karen Hicks, Team Leader
Chemistry and Toxicology Team
Product Science Branch
Antimicrobials Division (7510C)

Michele E. Wingfield, Chief
Product Science Branch
Antimicrobials Division (7510C)

Applicant: Avecia Inc.

FORMULATION FROM LABEL:

<u>Active Ingredient(s):</u>	<u>% by wt.</u>
N-butyl-1,2-benzisothiazolin-3-one	45.00
<u>Other Ingredient(s):</u>	55.00
Total:	100%

BACKGROUND: The applicant has submitted an application for registration for its product, Densil DG45, which is a formulated dilution of the technical grade N-butyl-1,2-benzisothiazolin-3-one (VANQUISH Technical, EPA File Symbol No. 72674-EG). In support of its application the applicant has submitted toxicity studies for oral toxicity, dermal toxicity, primary skin irritation, and dermal sensitization. In a previous review of toxicity by the Agency, these studies and their findings were determined to be acceptable. The absence of studies for primary eye irritation and acute inhalation toxicity was noted to which the applicant now responds.

RECOMMENDATIONS (PSB findings):

1. The applicant, in response to the Agency's request for justification of the omission of the study for primary eye irritation, asserts the results of the primary dermal irritation study which showed the subject product as being corrosive to rabbit skin and classified toxicity category I, is a clear indication of the corrosive effect the product would have on eye contact. Therefore, the applicant requests a waiver of the primary eye irritation study and accepts a toxicity category I classification. The Agency grants to the applicant a waiver of the requirement to submit a primary eye irritation study and assigns category I to the product.
2. The applicant, in response to the Agency's request for justification of the omission of the study for acute inhalation toxicity, makes reference to the study, MRID #450830-04, which establishes the LC_{50} for male rats at >0.733 (mortality rate at 2/5); the LC_{50} for female rats at $>0.197 <0.733$ (mortality rate at 0/5 and 4/5, respectively). The test material of this study was identified as DS 6039 (45.2% N-butyl-1,2-benzisothiazolin-3-one in propylene glycol). The Agency finds the study to be not acceptable due to the comments below. Given the data gap between the two points, the lower of which showed no mortalities (0/10) and the higher of which showed an 80% mortality of the female rats (4/5) and a 40% mortality of the males, there are no findings to indicate the point at which the LC_{50} of the combined sexes is reached. The registrant must establish an LC_{50} of the combined sexes.
3. The applicant has satisfactorily identified the DS 6039 as being significantly equivalent to the subject material of this application, Densil DG45 Fungicide.

The acute toxicity profile for Reg. No. 72674-EA is currently:

acute oral toxicity	Acceptable	III
acute dermal toxicity	Acceptable	III
acute inhalation toxicity	Unacceptable	
primary eye irritation	Waived	I
primary skin irritation	Acceptable	I
dermal sensitization	Acceptable	Strong Sensitizer

LABELING:

1. The signal word is DANGER.
2. The Precautionary Statements must read:

CORROSIVE. Causes irreversible eye damage and skin burns. Wear protective clothing and gloves (coveralls worn over long-sleeved shirt and long pants, socks and chemical resistant footwear). Wear protective eyewear (goggles or face shield). Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove contaminated clothing and wash before reuse.

3. The First Aid Statements are acceptable.

DATA REVIEW FOR ACUTE INHALATION TOXICITY (§81-3, 870.1300)

Product Manager: Marshall Swindell

MRID No.: 450830-04

Reviewer: R. Turpin

Study Completion Date: 9/10/97

Report No.: HR2306

Testing Laboratory: Central Toxicology Laboratory

Author: N.J. Rattray

Quality Assurance (40 CFR §160.12): Statements disclosed

Test Material: DS6039

Concentration: 0.733 mg/L

Species: Rat

Weight: Males - 298-372 g.; Females - 222-243 g.

Age: 8-12 weeks

Source: Rodent Breeding Unit, Zenaca Pharmaceuticals

Summary:

1. **LC₅₀ (mg/L):**
Males = >0.733 mg/L
Females = >0.197<0.733 mg/L
Combined = >0.197<0.733 mg/L
2. **The estimated LC₅₀ is** >0.197<0.733 mg/L
3. **MMAD:** 1.49
4. **Tox. Category:** II **Classification:** Acceptable

Procedure (Deviation From §81-3): None noted.

Results:

Reported Mortality

Exposure Concentration	(NUMBER DEATHS/NUMBER TESTED)		
	Males	Females	Combined
0.733 mg/L	2/5	4/5	6/10
0.197 mg/L	0/5	0/5	0/10

Chamber Atmosphere			
Dose Level	MMAD	GSD	particles <
0.733 mg/L	1.49 μm	2.04 μm	63.6%
0.197 mg/L	1.65 μm	3.45 μm	86.6%

Chamber Environment	
Chamber Volume	27.6 L
Airflow	8-12 L/min
Temperature	18.6-21.1 °C
Relative Humidity	20-40%

Clinical Observations: In the 0.733 mg/L group, there were three mortalities. The remaining animals survived but three females were killed on day 4 due to severe clinical effects. There were no mortalities in the group exposed to the 0.197 mg/L concentration. Observations during exposure at 0.733 mg/L revealed wet fur, salivation, auditory hypoaesthesia, reduced breathing rate and increased breathing depth, labored breathing, and gasping. Some of the aforementioned effects were also observed among the animals exposed at the lower concentration of 0.197 mg/L. Post exposure, abnormalities including piloerection, hunched posture, chromodacryorrhea and wet fur were observed.

Gross Necropsy Findings: Upon post mortem examination abnormalities such as stained mouth, distended stomach and intestines with gas, dark lungs or dark areas on the lung,

Label Review System

PARTIAL LABEL

PRODUCT ID #: 072674-00026

PRODUCT NAME:

SIGNAL WORD: DANGER

Hazards to Humans and Domestic Animals:

Restricted Use Pesticide due to toxicity categories. For retail sale to and use only by Certified Applicators or persons under their direct supervision and only for those uses covered by the Certified Applicator's certification.

Corrosive. Causes irreversible eye damage. Causes skin burns. Harmful if swallowed. Harmful if absorbed through skin. Do not get in eyes or on clothing. Wear protective eyewear (goggles, face shield, or safety glasses). Wash thoroughly with soap and water after handling and before eating, drinking, chewing gum, or using tobacco. Remove contaminated clothing and wash before reuse. Do not get in eyes, on skin, or on clothing. Wear: Coveralls worn over long-sleeved shirt and long pants. Socks. Chemical-resistant footwear. Gloves. Remove and wash contaminated clothing before reuse. Avoid contact with skin, eyes or clothing. Wear: Long-sleeved shirt and long pants. Shoes.

Prolonged or frequently repeated skin contact may cause allergic reactions in some individuals.

First Aid:

If in eyes:

- Hold eye open and rinse slowly and gently with water for 15-20 minutes.
- Remove contact lenses, if present, after the first 5 minutes, then continue rinsing.
- Call a poison control center or doctor for treatment advice.

If swallowed:

- Call a poison control center or doctor immediately for treatment advice.
- Have person sip a glass of water if able to swallow.
- Do not induce vomiting unless told to by a poison control center or doctor.
- Do not give anything to an unconscious person.

If on skin:

- Take off contaminated clothing.
- Rinse skin immediately with plenty of water for 15-20 minutes.
- Call a poison control center or doctor for treatment advice.

-Have the product container or label with you when calling a poison control center or doctor or going for treatment.

Note to Physician: Probable Mucosal Damage May Contraindicate the Use of Gastric Lavage.

ACUTE TOX ONE-LINER

1. PC CODE: 98951

2. CURRENT DATE: 11/29/01

3. TEST MATERIAL: Densil DG45 Fungicide

Acute tox

Study/Species/Lab/ Study#/Date	MRID No.	Results	Tox. Cat.	Core Grade
acute oral toxicity/Rat/Central Toxicology Laboratory/AR6466/10-16-97	443649-15	LD ₅₀ (mg/kg) = <5000 mg/kg	III	A
acute dermal toxicity/Rat/Central Toxicology Laboratory/CR3381/9-19-97	443649-16	LD ₅₀ (mg/kg) = >2000 mg/kg	III	A
acute inhalation toxicity/Rat/Central Toxicology Laboratory/HR2306/9-10-97	450830-04	LC ₅₀ (mg/L) =		U
primary eye irritation/	Waived	Corrosive	I	A
primary skin/irritation/Rabbit/Central Toxicology Laboratory/EB4611/10-6-97	443649-17	Corrosive	I	A
dermal sensitization/Guinea pig/Central Toxicology Laboratory/GG6967/10-6-97	443649-18	Strong sensitizer	---	A

A = Acceptable
 U = Unacceptable
 S = Supplementary
 V = self-Validated